

**REMARKS/ARGUMENTS**

With this amendment, Claims 1, 3-7 and 9-57 are pending. Claims 10-19 and 22-57 are cancelled without prejudice. Claims 1, 3-7, 9 and 20-21 are rejected. For convenience, the Examiner's rejections are addressed in the order presented in the October 22, 2002, Office Action.

**I. Status of the Claims**

Claims 1, 3-7, 9 and 20-21 are currently under examination and are rejected.

**II. Rejections under 35 U.S.C. §102(a)**

Claims 1, 3-7 and 9 are rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Shimada *et al.* (*Cytogenet. Cell. Genet.* 83:232-235 (1998)). Applicants respectfully traverse the rejection. Under 35 U.S.C. §102(a) "[a] person shall be entitled to a patent unless--(a) the invention was . . . described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent. . . ." Courts have defined the phrase 'printed publication' as follows: "The statutory phrase 'printed publication' has been interpreted to mean that before the critical date the reference must have been sufficiently accessible to the public interested in the art; dissemination and public accessibility are the keys to the legal determination whether a prior art reference was 'published'." *Constant v. Advanced Micro-Devices* 848 F.2d 1560 1568 (Fed. Cir. 1988). Thus, a publication sent by mail, such as a technical journal, has an effective publication date as of the date it was first received by a member of the public, not the date it was mailed or sent to the publisher. MPEP §2128.02.

In order to be considered prior art under §102(a), a printed publication must have been publicly available before the invention date of the Applicant. In the U.S., with out other evidence, the earliest effective filing date for filing the application is

presumed to be the constructive invention date. Thus, a journal published (*e.g.*, received by a member of the public) after February 26, 1999, the earliest effective priority date of the application, is not prior art for the current application under 35 U.S.C. §102(a).

Although there is no evidence that the Shimada reference was received by a member of the public before February 26, 1999, the Office Action alleges that the reference was accepted by a journal and, therefore, published in October 1998.

According to the MPEP, an applicant can submit evidence to prove the date a reference became publicly accessible and therefore “published.” MPEP §2128.02 *citing Constant*, 848 F.2d at 1569. In support of a publication date after February 26, 1999, Applicants submit an e-mail message from Carmen Scaglia of the Rights and Permissions Department of S. Karger AG, the publisher of the Shimada reference to demonstrate that the Shimada reference was published after February 26, 1999, the earliest effective priority date of the application. (See, Exhibit A.) Ms. Scaglia verifies that the publication date (*e.g.* date of release of the journal to the public, not the legal standard for publication) of the reference is March 4, 1999. Shimada *et al.* could not have been received by a member of the public before March 4, 1999, and thus the reference was not published under the legal standard before February 26, 1999, the earliest effective priority date of the application. Because Shimada *et al.* did not meet the legal standard for publication before the earliest effective priority date of the application, it is not properly cited as prior art. In view of the submitted evidence, Applicants respectfully request that the rejection under 35 U.S.C. §102(a) be withdrawn.

### **III. Rejections under 35 U.S.C. §102(b)**

Claims 1, 3-7, 9 and 20-21 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Bonaldo *et al.* (*Genome Research* 6:791-806 (1996)). To anticipate a claim, the reference must teach every element of the claim. To do so, the reference must contain an enabling disclosure of the claimed invention.

Bonaldo *et al.* disclose methods of making directionally cloned, normalized cDNA libraries. Bonaldo *et al.* disclose only DNA sequences of library vectors, or oligonucleotides used for directional cloning, *e.g.*, sequences that are common to all library members. The 1996 Bonaldo reference does not disclose a sequence of a specific ING2 nucleic acid, and furthermore does not disclose any ING2 sequence that would hybridize to SEQ ID NO:2 under stringent conditions. At best Bonaldo *et al.* provides only a general method of making a cDNA library and cloning cDNA inserts. In contrast, the claimed invention is a genus of nucleic acid molecules that encode a novel ING2 tumor suppressor protein and hybridize to a specific novel reference sequence, *e.g.*, SEQ ID NO:2.

Applicants respectfully traverse the rejection under 35 U.S.C. §102(b). Bonaldo *et al.* does not contain an enabling disclosure and is therefore not properly cited as prior art. In addition, Bonaldo *et al.* does not expressly or inherently describe all the elements of the claimed invention.

A. *Bonaldo et al. is not an enabling reference and therefore is not properly cited as prior art.*

The Federal Circuit has repeatedly ruled that in order to anticipate an invention, a prior art reference must contain an "enabling disclosure." *In re Hoeksema*, 158 USPQ 596, 600 (CCPA 1968). The proper test of an enabling description in a publication cited under §102(b) is:

whether one skilled in the art to which the invention pertains could take the description of the invention in the printed publication and combine it with his own knowledge of the particular art and from this combination be put in possession of the invention on which a patent is sought. *Id.*, and *In re LeGrice*, 301 F.2d 929, 939 (C.C.P.A. 1962).

The claimed invention is a genus of ING2 nucleic acid sequences, *e.g.*, chemical compounds. Courts have developed a body of case law regarding the information required to provide an enabling disclosure of a chemical compound. In order

to place a chemical compound in possession of the public, the disclosure must be such that one of ordinary skill in the art could at once envisage the compound. *In re Donohue*, 207 USPQ 196, 199 (Fed Cir. 1980) and *In re Petering*, 133 USPQ 275, 279-280 (C.C.P.A. 1962). In addition, the reference must disclose a method of making the compound. *In re Hoeksema*, 158 USPQ at 601.

1. Based on the disclosure of Bonaldo *et al.*, one of skill would not be able to at once envisage the claimed chemical compounds.

In order to place a chemical compound in possession of the public, the disclosure must be such that one of ordinary skill in the art could at once envisage the compound. *In re Donohue*, 207 USPQ 196, 199 (Fed Cir. 1980) and *In re Petering*, 133 USPQ 275, 279-280 (C.C.P.A. 1962). The Federal Circuit has ruled that for genetic material, one of skill cannot visualize or recognize the a genus unless a DNA sequence or other common structural feature is provided. See, e.g., *University of California v. Eli Lilly*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicants assert that the disclosure of Bonaldo *et al.* does not allow one of skill to at once envisage the claimed ING2 nucleic acid sequences and is therefore not an enabling reference. In order to allow one of skill to at once envisage a specific nucleic acid sequence, a reference must provide the structure of the nucleic acid. Bonaldo *et al.* does not provide the structure, e.g., the sequence, of an ING2 nucleic acid that will hybridize to SEQ ID NO:2 under stringent conditions. Bonaldo *et al.* disclose only DNA sequences of library vectors, or oligonucleotides used for directional cloning, e.g., sequences that are common to all library members. Because Bonaldo *et al.* lacks the sequence information necessary to enable one of skill to at once envisage the claimed invention, Bonaldo *et al.* is not an enabling reference and is improperly cited as prior art.

2. Based on the disclosure of Bonaldo *et al.*, one of skill would not be able to make the claimed invention.

Bonaldo *et al.* also fails to enable the claimed inventions because the reference does not provide a method of making the claimed ING2 nucleic acids. The Federal Circuit has repeatedly ruled that general cloning methods, such as those disclosed in Bonaldo *et al.*, are not sufficient to describe how to make a particular DNA sequence, such as an ING2 nucleic acid of the claimed genus. The Federal Circuit has provided a legal standard for information necessary to conceive a method of making a nucleic acid and, by analogy, the information necessary to disclose a method of making a nucleic acid. According to the Federal Circuit, both conception of a nucleic acid structure and a method of making a nucleic acid occur simultaneously with disclosure of the DNA sequence. *See Amgen v. Chugai*, 927 F.2d 1200 (Fed. Cir. 1991); *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993); *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993); and *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995). Thus, in order to disclose a method of making a specific nucleic acid or genus of nucleic acids, a specific DNA sequence must be provided.

As described above, the only DNA sequences provided by Bonaldo *et al.* are vector sequences or oligonucleotides useful for general cDNA library construction, not specific ING2 nucleic acid sequences that will hybridize to SEQ ID NO:2 under stringent conditions, as is claimed. Because Bonaldo *et al.* does not provide a specific ING2 DNA sequence that will hybridize to the claimed reference nucleic acid, Bonaldo *et al.* does not disclose a method of making the claimed nucleic acids and thus, is not an enabling reference.

Bonaldo *et al.* does not provide an enabling description of either the structure of the claimed ING2 nucleic acids or a method specifically to make the claimed ING2 nucleic acids, and thus, is not an enabling reference. Applicants therefore respectfully request that the rejection because of alleged anticipation in view of Bonaldo *et al.* be withdrawn

*B. Bonaldo et al. does not expressly or inherently describe the claimed nucleic acid sequences, and thus, does not anticipate the claimed invention.*

To anticipate a claim, the reference must teach every element of the claim. “A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

*Bonaldo et al.* does not expressly or inherently describe all the elements of the claimed invention and thus cannot anticipate the claimed invention under 35 U.S.C. §102(b).

1. *Bonaldo et al.* does not expressly teach all the elements of the claimed invention.

In an Office Action dated December 18, 2001, the Examiner alleged that *Bonaldo et al.* taught an isolated nucleic acid encoding a polypeptide with greater than 70% amino acid identity to SEQ ID NO:1. After careful reading of the cited reference, Applicants were unable to locate any such ING2 nucleic acid or amino acid sequence and respectfully request the Examiner to identify the page number of the 1996 *Bonaldo et al.* reference disclosing that information. Applicants also respectfully remind the Examiner that GenBank Accession No. BF523624, was not submitted until December 11, 2000, well after the earliest priority date of the application, and that the contents of that submission may not be cited as prior art.

Because *Bonaldo et al.* does not expressly describe all the elements of the ING2 nucleic acids of the claimed invention, *Bonaldo et al.*, does not anticipate the claimed invention.

2. Bonaldo et al. does not inherently teach all the elements of the claimed invention.

In an Office Action dated December 18, 2001, the Examiner appears to allege that Bonaldo *et al.* inherently described the claimed invention. The Examiner alleged that because the libraries of Bonaldo *et al.* were PCR amplified, the reference taught an isolated nucleic acid that inherently comprises a DNA sequence that specifically hybridizes to an ING2 sequence of SEQ ID NO:2. That rejection was maintained in the present Office Action.

Bonaldo *et al.* discloses four general methods of preparing normalized cDNA libraries. Only Method 4 includes a PCR amplification step, done using T7 and T3 primers that hybridize to vector sequences. Applicants respectfully remind the Examiner that T7 and T3 primer sequences were originally derived from bacteriophage. The T7 and T3 primers are the only PCR primer sequences disclosed in the reference and they do not hybridize to SEQ ID NO:2 under stringent conditions or encode p33ING2, as is required by the claims. The reference provides no information on specific ING2 DNA sequences that hybridize under stringent conditions to a SEQ ID NO:2.

To establish inherency, the missing descriptive matter must be present in the thing described in the reference so that its presence would be recognized by person of ordinary skill in the art. MPEP §2112 and *In re Robertson*, 49 USPQ2d 1949, 1950-1 (Fed. Cir. 1999). Claims to products "cannot be predicated on mere conjecture respecting the characteristics of products that might result from the practice of processes disclosed in references." *W. L. Gore v. Garlock, Inc.* 220 USPQ 303, 314 (Fed. Cir. 1983). The asserted inherency must be based in fact or technical reasoning "to support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP §2112. No inherency is found in an undisclosed element that is only present by virtue of an "intervening step of human perception, awareness and understanding." *Hughes Aircraft Co. v. U.S.* 8 USPQ2d 1580, 1583 (U.S. Claims 1988).

**a. One of skill in the art would not recognize the presence of a particular nucleic acid without knowing the DNA sequence.**

A prior art reference that inherently, rather than expressly, discloses a claim element must make clear to one of skill in the art that the missing element is necessarily contained in the thing described. MPEP §2112. Under that standard, Bonaldo *et al.* must provide sufficient description to make clear to one of skill that an ING2 DNA (an unknown DNA sequence at the time of the 1996 Bonaldo *et al.* reference) is present when cDNA libraries are made using the disclosed methods. Bonaldo *et al.* does not do so.

Bonaldo *et al.* discloses only general methods to make expression libraries and does not disclose a specific ING2 DNA sequence that would hybridize to SEQ ID NO:2. In order to know that a specific nucleic acid molecule is in a library, one of ordinary skill in the art must, at a minimum, know the DNA sequence of the nucleic acid of interest. One of skill in the art would not recognize the presence of a previously unknown nucleic acid in an expression library, merely on learning that an expression library has been constructed. Because the reference does not allow one of skill to recognize the presence of an ING2 nucleic acid that hybridizes to SEQ ID NO:2, the reference does not inherently disclose such a nucleic acid.

**b. Disclosure of a general cloning method does not provide disclosure of a specific non-vector DNA sequence.**

The inherency asserted by the Office Action does not necessarily flow from the teachings of Bonaldo *et al.* Bonaldo *et al.* teach a general method of making cDNA libraries. The presence of specific nucleic acids (*i.e.*, ING2 nucleic acids) in the cDNA libraries cannot be predicted before the cDNA inserts have been sequenced, particularly previously unknown or sequenced nucleic acids.



In a previous Office Action, the Examiner appears to allege that the nucleic acids of Bonaldo *et al.* inherently comprise nucleic acids that hybridize to SEQ ID NO:2 because the library sequences were PCR amplified. Applicants reiterate, Bonaldo *et al.* provide no specific ING2 nucleic acid sequence, either expressly or inherently. The only specific hybridization sequences provided by the authors are thus T3 and T7 PCR primers, common to all vectors in the library. However, the recognition that a specific non-vector nucleic acid is present in a given cDNA library requires an intervening step of "human perception, awareness and understanding." *Hughes, supra*. The particular intervening step is determination of the DNA sequence for the specific non-vector nucleic acid. The authors of Bonaldo *et al.* did not disclose performance of that intervening step by providing specific cloned sequences, and therefore the disclosure of Bonaldo *et al.* does not inherently contain any specific non-vector DNA sequence. In contrast, Applicants were the first to independently isolate and sequence a cDNA that encodes ING2. Applicants' contribution to biological science is deserving of patent protection and should be recognized as such.

Bonaldo *et al.* is not an enabling reference, and does not expressly or inherently teach all the elements of the claimed invention. In view of the above arguments and remarks, Applicants respectfully request that the rejection for alleged anticipation under 35 U.S.C. §102(b) be withdrawn.

#### **IV. Rejections under 35 U.S.C. §103(a)**

Claims 1-9, 20-21 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Shimada *et al.* The Office Action alleges it would have been *prima facie* obvious to one of ordinary skill in the art to include an expression vector and host cell with the teachings of Shimada *et al.*

Applicants respectfully traverse. As described above, Shimada *et al.* is not prior art because it was not received by a member of the public, and thus, not published,

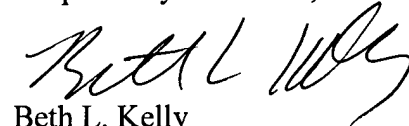
until after the earliest effective filing date of the application. Thus, the rejection under 35 U.S.C. §103(a) was made improperly and Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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